

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 20-237/S-007

CHEMISTRY REVIEW(S)

Blay
HFD-540

DEC 2 1997

DIVISION OF DERMATOLOGICAL AND DENTAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-237 CHEM.REVIEW #: 1 REVIEW DATE: 24-Nov-97

<u>SUBMISSION/TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
Eff.Suppl. SE1-007,	11-Feb-97	12-Feb-97	18-Feb-97
Eff.Suppl. SE1-007/BL, (Amendment 4)	08-May-97	09-May-97	13-May-97
Suppl. 20-237/SE1-007/BC,	14-Nov-97	17-Nov-97	21-Nov-97

NAME & ADDRESS OF APPLICANT:

MGI Pharma, Inc.
Suite 300E, Opus Center
9900 Bren Road East
Minnetonka, MN 55343
ATTN: Jo H. Gustafson, Ph.D.
Director, Regulatory Affairs
Telephone: (612) 935-7335
Fax: 612-935-0468

DRUG PRODUCT NAME

Proprietary:

Nonproprietary/USAN:

Salagen® Tablets
Pilocarpine Hydrochloride

Code Names/ #'s:

Chemical Type:

Therapeutic Classes:

3P

ANDA Suitability Petition/DESI/Patent Status: NOT APPLICABLE!

PHARMACOLOGICAL CATEGORY/INDICATION: For treatment of symptoms of dry mouth and dry eyes in patients with Sjogren's Syndrome.

DOSAGE FORM:

Tablets

STRENGTHS:

5 mg

ROUTE OF ADMINISTRATION:

Oral

DISPENSED:

☒ X ☐ Rx ☐ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:
2(3H)-Furanone, 3-ethylidihydro-4-[(1-methyl-1H-imidazol-5-yl)methyl]-monohydrochloride, (3S-cis)

Molecular Formula:

C₁₁H₁₆N₂O₂

Molecular Weight:

208.26

CAS No.:

92-13-7

SUPPORTING DOCUMENTS:

REMARKS/COMMENTS:

This Efficacy Supplement required that two CMC issues be reviewed, i.e.

1) Additional 18-24 month stability data was added for four drug product lots, i.e. Salagen Tablet Lots# CP00A, CP29M, CR92M and CR93M;

2) An Abbreviated Environmental Assessment (AEA) was submitted in support of sponsor's expanded indication for Salagen Tablets, i.e. to include the treatment of xerostomia and keratoconjunctivitis sicca in patients with Sjogren's Syndrome. However, there is a possibility that MGI Pharma may be eligible for a categorical exclusion and thus by-pass the AEA process. Project Management was informed and will follow-up.

The categorical exclusion follow-up resulted in sponsor submitting NDA Supplement 20-237/SE1-007/BC which claimed an exclusion based upon an EIC of 0.003071 ppb.

1) STABILITY DATA

The additional stability data for all eight of the Salagen Tablets (pilocarpine hydrochloride), 5 mg, which include the above four lots are provided below:

<u>LOT#</u>	<u>Mfgr'd. Date</u>	<u>Stability Conditions</u>	<u>Length of Stability Study</u>	<u>Results¹</u>
CP 00A	8/3/94	25°C	24 Months	ACCEPTABLE
CR 93M	11/30/94	25°C	24 Months	ACCEPTABLE
CR 93M	11/30/94	40°C/75%RH	6 Months	ACCEPTABLE
CR 92M	11/29/94	25°C	24 Months	ACCEPTABLE
CR 92M	11/29/97	40°C/75%RH	6 Months	ACCEPTABLE
CP 29M	2/10/97	25°C	24 Months	ACCEPTABLE
CP 29M	8/30/94	40°C/75%RH	6 Months	ACCEPTABLE

¹The following are the stability-indicating tests conducted for each of these time period at ambient/25°C temperatures: baseline, 3, 6, 9, 12, 18 and 24 months. The time periods for accelerated temperature conditions include: baseline, 1,2,3 and 6 month periods.

- APPEARANCE: White, Round Coated Tablets.
- ASSAY: % Pilocarpine.
- DISSOLUTION: NLT % dissolved in minutes.
- TOTAL RELATED COMPOUNDS: NMT 2.0%
 - Isopilocarpine HCl: NMT %
 - Pilocarpic Acid: NMT %
 - Isopilocarpic Acid: NMT %
 - Unspecified: NMT %

Based upon only the above stability data, these Salagen Tablets are recommended for an expiry date of 30 months. As additional stability data becomes available, this expiration date can be extended.

Informational Request: USP defines "controlled room temperature as a temperature maintained thermostatically between 15°C and 30°C (59°F and 86°F). Future stability studies conducted at room temperatures/ambient temperatures should be conducted at 25°C \pm 2°C and 60% relative humidity.

2) ENVIRONMENTAL ASSESSMENT

MGI Pharma was contacted by Project Management on 10/27/97 to submit an Environmental Assessment categorical exclusion IF the estimated concentration of the active moiety at the point of entry into the aquatic environment is < 1 ppb which is equivalent to \approx 40,700 kgs of active moiety per year. As stated previously, NDA Supplement 20-237/SE1-007/BC was submitted and claimed a categorical exclusion in accordance with 21 CFR 25.15(d). Their categorical exclusion was based upon an EIC calculated aquatic contamination of 0.003071 ppbs which is well below the required < 1.0 ppb required for a categorical exclusion claim.

CONCLUSIONS & RECOMMENDATIONS:

Both the Environmental Assessment categorical exclusion and the additional stability data are recommended for APPROVAL. However, this product is recommended with an expiration date of 30 months. As additional acceptable stability data becomes available, this expiration date can be extended.

James D. Vidra, Ph.D.
Review Chemist

cc: ^{NDA} Orig. IND# 20-237
HFD-540/Division File
HFD-540/ProjMan/Blay
HFD-540/Pharm/See
HFD-540/MedOff/Hyman
HFD-540/BioPharm/Bashaw
HFD-540/Chm/Vidra
HFD-540/ChmTeamLdr/DeCamp
HFD-830/ChmDivDir/Chen
filename: N20237.sel

12/2/97

✓ 12/20/97

1244
540

NOV 14 1997

DIVISION OF DERMATOLOGICAL AND DENTAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-237 CHEM.REVIEW #: 1 REVIEW DATE: 28-Oct-97
SUBMISSION/TYPE DOCUMENT DATE CDER DATE ASSIGNED DATE
NC 23-Sep-97 24-Sep-97 29-Sep-97

NAME & ADDRESS OF APPLICANT:

MGI Pharma, Inc.
Suite 300E, Opus Center
9900 Bren Road East
Minnetonka, Minnesota 55343-9667
ATTN: Jo H. Gustafson, Ph.D.
Director, Regulatory Affairs
Telephone: 612-935-7335
FAX: 612-935-0468

DRUG PRODUCT NAME

Proprietary:

Salagen® Tablets

Nonproprietary/USAN:

Pilocarpine Hydrochloride

Code Names/ #'s:

Chemical Type:

Therapeutic Classes:

3P

ANDA Suitability Petition/DESI/Patent Status: NOT APPLICABLE!

PHARMACOLOGICAL CATEGORY/INDICATION: Treatment of xerostomia induced
by radiation therapy for head and
neck cancers.

DOSAGE FORM:

Tablet

STRENGTHS:

5 mg

ROUTE OF ADMINISTRATION:

Oral

DISPENSED:

☒ X Rx ☐ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:
2(3H)-Furanone, 3-ethylidihydro-4-[(1-methyl-1H-imidazol-5-yl)methyl]-
monohydrochloride, (3S-cis)

Molecular Formula:

208.26 (as pilocarpine)
244.86 (as pilocarpine
hydrochloride)

Molecular Weight:

C₁₁H₁₆N₂O₂.HCl

CAS No.:

NDA 20-237
MGI Pharma, Inc.
Salagen Tablet, 5mg

Page 2 of 2

SUPPORTING DOCUMENTS:

NDA 20-237/SE1-006
FDA Approval Letter, dated 3/11/97

REMARKS/COMMENTS:

As requested in FDA's March 11, 1997 Approval Letter, MGI Pharma submitted one box of currently marketed 100-5 mg Salagen Tablets (pilocarpine hydrochloride) containing an updated package insert. The box labeling with insert were reviewed only for its two CMC Sections, i.e. the Description and How Supplied? Sections, and found ACCEPTABLE.

No action is required. The attached drug should be disposed of through normal safety channels.

/S/

James D. Vidra, Ph.D.
Review Chemist

cc: Orig. NDA# 20-237
HFD-540/Division File
HFD-540/ProjMan/Blay
HFD-540/Chem/Vidra
HFD-540/TeamLdr/DeCamp

14/97

filename: N20237.sel